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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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12/05/2003

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EXAMINER

LIU, SUE XU

ART UNIT

PAPER NUMBER

1639

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/728,355	<b>Applicant(s)</b> WATSON MICHNICK ET AL.	
	<b>Examiner</b> SUE LIU	<b>Art Unit</b> 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 February 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5,8,11-14,17,20,21,24,30-33 and 37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5,8,11-14,17,20,21,24,30-33 and 37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Claim Status***

1. Claims 6, 7, 9, 10, 15, 16, 18, 19, 22, 23, 25-29 and 34-36 have been cancelled as filed on 6/5/07.

Claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 and 37 are currently pending.

Claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 and 37 are being examined in this application.

### ***Election/Restrictions***

2. Applicant's election with traverse of Group I (claims 1-5, 8, 11-14, 17, 20-24, 29-33 and 37) in the reply filed on 5/8/06 is as previously acknowledged.

### ***Priority***

3. This application claims priority benefit as a CIP of U.S. Patent Application Nos. 09/603,885 (filed 6/26/2000), which is now a US PATENT, 6,897,017 (5/24/2005). The US PATENT, 6,897,017 is a CIP of US Patent Application Nos. 09/017,412 (filed 2/02/1998), which is now a US PATENT, 6,270,964 (8/7/2001). This application also claims priority to U.S. Provisional Patent Application Nos. 60/141,210, filed 6/26/1999.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 35 U.S.C. 120, 121, or 365(c) as follows:

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The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/603,885 and 09/017,412, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant application claims methods for identifying an interacting set of molecules using green fluorescent protein or mutants thereof as reporter molecules, which are not methods disclosed by the parent US Application No. 09/603,885 (filed 6/26/2000). The US application 09/603,885 (filed 6/26/2000) only disclosed a method of identifying an interacting set of molecules using DHFR as the reporter enzyme. Therefore, the parent application does not provide support for the instant claimed method of using a fluorescent protein as a reporter molecule.

The '885 application claims priority benefit to the grandparent application (09/017,412,; filed on 2/2/1998; now patented as US 6,270,964), which also does not provide adequate support for the claimed methods of identifying an interacting set of proteins using green fluorescent protein (or broadly using fluorescent protein) or mutants thereof. The only relevant passage in the '412 application is a prophetic discussion of the possibility of using GFP. For example, at cols.23-24 of the '964 patent (parent of the '412 application), the passage recites "Recently the

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structure of GFP has been solved by two groups, making it now a candidate for a structure-based PCA-design [*sic*], which we have begun to develop” (‘964 patent, col.24, lines 13+). That is applicants have not, at the time of filing of the ‘964 patent, developed the specific structures for the fragmented GFP (or mutants thereof), or fluorescent protein in general that can be reconstituted for the purpose of detecting protein-protein interactions. The recitation of using GFP (or mutants) or fluorescent protein (or mutants) in general in the ‘964 patent is only prophetic in nature. Thus, as evidenced by the cited passage from the parent application (‘412), applicants are not in possession of the claimed methods of using GFP or broadly using fluorescent protein in general or mutants thereof.

See *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021 ("it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property ... because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated."). Here, Applicants have not provided any chemical structure, method of preparation, or physical/chemical properties for the claimed green fluorescent protein/mutant fragments. Thus, conception, within the meaning of *Amgen*,

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has not been achieved. In fact, Applicants admit that they have only “begun” to work on this project supporting the conclusion that a successful completion of this project had not yet been achieved.

Therefore, the instant application would not obtain the priority benefit of the earlier filed applications, 09/603,885 and 09/017,412.

Thus, the effective filing date of the instant application is 12/5/2003.

*Discussion and Answer to Argument*

4. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue the instant application should be granted the priority benefits of the parent applications (i.e. 09/603,885 (US PAT 6,897,017) and 09/017,412 (US PAT 6,270,964).*

*Applicants assert “the GFP species is indeed disclosed in the grandparent application (09/017,412)” and the ‘412 application “does provide support for the instant claimed method of using a fluorescent protein as a reporter molecule”. (Reply, pp.13-14).*

*Applicants also argue the ‘964 patent (i.e. the ‘412 application) contains granted claims drawn to using “a fluorescent protein”, and thus the ‘412 application must have possession of the “green fluorescent protein”. (Reply, pp.14+). Applicants also pointed to another granted patent, US 7,166,424, which also claims priority benefit to the ‘412 application, and having claims drawn to “a fluorescent protein”. (Reply, pp.15-16).*

Applicants' discussion of the granting of the grandparent application ('412) and the '424 patent is not found persuasive. Applicants have not clearly point out supports in the parent applications (i.e. '885 and '412) for the instant claimed method of using "green fluorescent protein" (GFP) or mutants thereof in a method where fusion proteins comprising fragments of the GFP are used in reconstitution assays.

In addition, each individual US patent application is examined separately, and the merits of teach case is also treated separately. "See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis")" (MPEP 2163).

*Applicants also state: "The issue is not an issue of prophetic possibility. The issue is 'Is the inventor in possession of the invention in his creative thoughts of how to use GFP and generate fragments for use in the protein complementation assay and how it would work and will it work'*

*Clearly, it has been shown by the Applicant himself by filing CIP's as well as all the copycats (much later filing dates than Applicant's priority date) such as those mentioned in the 35 USC 102 and 103 rejections below that the **vision of inventor Michnick in selecting fluorescent proteins as reporters has been proven correct.**" (emphasis in original; Reply, p.17).*

By applicant's own statement supra, it is clear that applicants are NOT in possession of the instant claimed method of using GFP fragments until the filing of the instant application (i.e. the CIP of the parent cases). Applicants have not provided any evidence to show possession and/or enablement for the instant claimed invention of using GFP fragments, prior to or at the

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time of filing of the parent applications. In other words, the disclosure of the instant application and the “copycats” all have later dates than the parent applications, and thus these later disclosures cannot be used as supporting evidence for the earlier filed parent applications.

*Applicants also provided the following reasons for support of the instant claimed invention using GFP fragments (in the form of fusion proteins) in reconstitution assays in the grandparent application (‘412 application):*

*“(1) As shown in the parent U.S. patent No. 6,270,964; in particular cols. 3 and 4 there is a complete description of how to design a PCA and how to select reporter proteins and enzymes. Starting in col. 3, line 58 and ending in col. 5, line 64, there is ample enablement on how to design protein reporters.” Applicants also quoted the cited passages in the Reply. (Reply, pp.17+).*

*“(2) As shown starting in col. 23, line 65 to col. 24, line 22 of the parent U.S. patent No. 6,270,964; regarding the fluorescent protein embodiment...” Applicants’ quotation of the cited passage omitted. (Reply, pp.19+).*

In regard to applicants’ listed first reason: The quotation starting at col.3, line 58 of the ‘964 patent (or the ‘412 application) provides a general and prophetic discussion of the PCA (i.e. protein-fragment complementation assay). The said passage does NOT provide common core structure and/or function for all of the protein/enzymes that can be used in PCA. The said passage does NOT show that GFP share a common core structure and/or function with the other proteins/enzymes that were successfully used in PCA. More importantly, the said passage does NOT describe the specific GFP fragments and/or fusion proteins comprising the said fragments



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that can be used in PCA. For example, the quoted passages state one general characteristic of the proteins used in PCA “A protein or enzyme that is relatively small” (e.g. col. 3, line 60) or have molecular weight between 10-40 kDa (col.4, lines 11+), which generic description can fit hundreds of proteins/enzymes and does NOT provide specific support for the instant claimed GFP.

In regard to applicants’ listed second reason: As discussed in the previous Office action, the quotation starting at col.23, line 65 of the ‘964 patent (or the ‘412 application) provides a general and prophetic discussion of GFP and possibilities of using GFP in PCA. For example, the ‘964 patent states the following (which applicants also quoted in the Reply): “Recently the structure of GFP has been solved by two groups, making it now a candidate for a structure-based PCA-design [*sic*], ***which we have begun to develop***” (‘964 patent, col.24, lines 13+). Clearly, the “conception” of the idea of using GFP in PCA type of assay has not been completed, rather the “conception” has just begun at the time of filing of the ‘412 application.

See MPEP 2163: “Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.”

In addition, the case laws define the concept of “Conception” as “Conception has been defined as “the complete performance of the mental part of the inventive act” and it is “the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention as it is thereafter to be applied in practice...” Townsend v. Smith, 36 F.2d 292, 295, 4 USPQ 269, 271 (CCPA 1930). “[C]onception is established when the invention is made sufficiently clear to enable one skilled in the art to reduce it to practice without the exercise

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of extensive experimentation or the exercise of inventive skill." *Hiatt v. Ziegler*, 179 USPQ 757, 763 (Bd. Pat. Inter. 1973). Conception has also been defined as a disclosure of an invention which enables one skilled in the art to reduce the invention to a practical form without "exercise of the inventive faculty." *Gunter v. Stream*, 573 F.2d 77, 197 USPQ 482 (CCPA 1978). See also *Coleman v. Dines*, 754 F.2d 353, 224 USPQ 857 (Fed. Cir. 1985) (It is settled that in establishing conception a party must show possession of every feature recited in the count, and that every limitation of the count must have been known to the inventor at the time of the alleged conception. Conception must be proved by corroborating evidence.); *Hybritech Inc. v. Monoclonal Antibodies Inc.*, 802 F. 2d 1367, 1376, 231 USPQ 81, 87 (Fed. Cir. 1986) (Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice."); *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001) (Inventor's "hope" that a genetically altered yeast would produce antigen particles having the particle size and sedimentation rates recited in the claims did not establish conception, since the inventor did not show that he had a "definite and permanent understanding" as to whether or how, or a reasonable expectation that, the yeast would produce the recited antigen particles.).” (MPEP 2138.04; emphasis added).

In this case, the ‘412 application only provides “inventor’s ‘hope” that the GFP fragments would work in PCA without a “definite and permanent understanding”. Thus, by applicants’ own statement in the ‘412 application, the complete conception of the invention of using fragmented GFP for PCA has not been achieved at the time of filing of the ‘412 application. In addition, Applicants have not provided any chemical structure, method of preparation, or physical/chemical properties for the claimed green fluorescent protein/mutant

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fragments. Thus, conception, within the meaning of *Amgen* (see above), has not been achieved.

*Applicants also cited several references to indicate the knowledge regarding GFP. (Rely, pp.20+).*

The question here is not whether applicants have possession of GFP, rather the question is whether applicants have possession of using the appropriate GFP fragments as parts of fusion proteins in a screening assay that requires full functional reconstitutions of the said GFP fragments. There is no question of using the full length GFP as a reporter molecule by itself. However, the instant application is claiming a method of using GFP fragments that can be reconstituted as fluorescent reporter molecule. Applicants have not demonstrated that the combination of cited references indicate fragmenting GFP and using fusion proteins comprising the GFP fragments in a screening assay are predictable at the time of the filing of the grandparent application ('412).

Thus, in view of the discussion supra, the instant application's claims of priority to the parent applications (i.e. '885 and '412 applications) are not granted.

***Claim Objection(s) / Rejection(s) Withdrawn***

5. In light of applicant's amendment the instant claim 37, the following claim objection as set forth in the previous office action is withdrawn:

Claim 37 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim 37 is not been further treated on the merits.

***Claim Objection(s) / Rejection(s) Maintained***

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(Note: the instant claim numbers are in bold font.)

*Umezawa WO*

7. Claims 1-3, 8, 11-13, 17, 20, 21, 24, 30-33 and 37 are rejected under **35 U.S.C. 102(b)** as being anticipated by Umezawa et al (PCT/JP00/09348; WO 02/08766; 1/31/02; The complete WO document is in Japanese except for the Abstract. The English equivalent, US 20030003506 (a 371 of PCT/JP00/09348) is relied upon for the specific teaching of the WO documents. The relevant citations discussed below correspond to the US 20030003506 document.). The previous rejection over claims 1-3, 8, 11-13, 17, 20, 21, 24, 30-33 is maintained for the reasons of record as set forth in the Office action as well as for the reasons below. The rejection over claim 37 is necessitated by applicant's amendment to the claims.

The instant claims recite a method for identifying an interacting set of proteins comprising: A) generating first and second fragments of a fluorescent protein reporter molecule which have a directly fluorescent detectable activity when reconstituted and/or associated,

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wherein said fluorescent protein is selected from the group consisting of green fluorescent protein and mutants of green fluorescent protein; B) coupling said first fragments of said green fluorescent protein or mutant green fluorescent protein reporter molecule to members of a first panel of proteins; C) coupling said second fragments of said green fluorescent protein or mutant green fluorescent protein reporter molecule to members of a second panel of proteins; D) mixing the products of B) and C); E) directly testing for fluorescence of said green fluorescent protein or mutant green fluorescent protein reporter molecule when reconstituted and/or associated; and F) identifying the protein panel members whose interaction resulted in fluorescence of said green fluorescent protein or mutant green fluorescent protein reporter molecule and which thus form an interacting set.

Umezawa et al, throughout the publication, teach methods of detecting protein and protein interactions for various proteins (Abstract). The reference teaches splitting a GFP protein into two fragments (e.g. Figure 1; [0020]; [0071]), which read on the generating first and second fragments of GFP of **clms 1-3, 8, 11-13, 17, 20, 21 and 24**.

The reference teaches attaching various proteins such as CaM and M13 proteins (e.g. Example 3), which each of the CaM and M13 protein can be considered as proteins or members of a first or a second panel of proteins according to the definition recited in the instant specification (e.g. p.15, lines 18+). The reference teaching of the specific proteins also read on the step of identifying a first and a second panel of proteins of **clms 2, 8, 12, 21 and 24**.

The reference teaches conjugating various proteins to each of the two fragments (e.g. Figure 1; Figure 4; [0005]; [0008]; [0018]; [0019]; [0020]; [0023]; [0024]; Example 2), which read on method steps B-F of **clms 1-3, 8, 11-13, 17, 20, 21 and 24** because the various proteins

attached to the fragments of GFP would be “members of a first (or second) panel of proteins”.

The reference teaches detecting the fluorescent signal of the reconstituted GFP (Example 3, especially [0087]), which reads on the optically detectable and fluorescent signals of **clms 30** and **31** as well as the fluorescent method of **clm 37**, and the inherent property of “generates a signal that can be quantified within living cells” and “can be localized within living cells” recited in **clms 32 and 33**.

Discussion and Answer to Argument

8. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue because Umezawa reference teaches the “indicator protein” is fused to “an intein polypeptide”, the Umezawa reference does not teach the instant claimed invention. (Reply, p.23).*

However, the instant claim language is broad and generic, and does not exclude the use of “an intein polypeptide”. Applicants are respectfully directed to the above rejection for detailed discussion of the reference's teachings.

Umezawa '506

9. Claims 1-3, 8, 11-13, 17, 20, 21, 24, 30-33 and 37 are rejected under **35 U.S.C. 102(a)** as being anticipated by Umezawa et al (US 20030003506; pub date 1/2/2003). The previous rejection over claims 1-3, 8, 11-13, 17, 20, 21, 24, 30-33 is maintained for the reasons of record

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as set forth in the Office action as well as for the reasons below. The rejection over claim 37 is necessitated by applicant's amendment to the claims.

Umezawa et al, throughout the publication, teach methods of detecting protein and protein interactions for various proteins (Abstract). The reference teaches splitting a GFP protein into two fragments (e.g. Figure 1; [0020]; [0071]), which read on the generating first and second fragments of GFP of **clms 1-3, 8, 11-13, 17, 20, 21 and 24**.

The reference teaches attaching various proteins such as CaM and M13 proteins (e.g. Example 3), which each of the CaM and M13 protein can be considered as proteins or members of a first or a second panel of proteins according to the definition recited in the instant specification (e.g. p.15, lines 18+). The reference teaching of the specific proteins also read on the step of identifying a first and a second panel of proteins of **clms 2, 8, 12, 21 and 24**.

The reference teaches conjugating various proteins to each of the two fragments (e.g. Figure 1; Figure 4; [0005]; [0008]; [0018]; [0019]; [0020]; [0023]; [0024]; Example 2), which read on method steps B-F of **clms 1-3, 8, 11-13, 17, 20, 21 and 24** because the various proteins attached to the fragments of GFP would be "members of a first (or second) panel of proteins".

The reference teaches detecting the fluorescent signal of the reconstituted GFP (Example 3, especially [0087]), which reads on the optically detectable and fluorescent signals of **clms 30, 31 and 37**, as well as the inherent property of "generates a signal that can be quantified within living cells" and "can be localized within living cells" recited in **clms 32 and 33**.

#### Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the

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following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue because Umezawa reference teaches the "indicator protein" is fused to "an intein polypeptide", the Umezawa reference does not teach the instant claimed invention. (Reply, p.23).*

However, the instant claim language is broad and generic, and does not exclude the use of "an intein polypeptide". Applicants are respectfully directed to the above rejection for detailed discussion of the reference's teachings.

Hamilton '701

11. Claims 1-5, 8, 11-14, 17, 20, 21, 24, and 30-33 are rejected under **35 U.S.C. 102(b)** as being anticipated by Hamilton et al (US 2002/0146701; 10/10/2002). The previous rejection over claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 is maintained for the reasons of record as set forth in the Office action as well as for the reasons below. The rejection over claim 37 is necessitated by applicant's amendment to the claims.

Hamilton et al, throughout the publication, teach a method of using GFP fragments to detect protein-protein interactions (Abstract). The reference teaches fragmenting GFP (e.g. [0055]+; [0061]; claim 22), which reads on the generating first and second fragments of GFP of **clms 1-3, 8, 11-13, 17, 20, 21 and 24.**

The reference teaches attaching various proteins such as leucine zipper proteins and proteins encoded by cDNA libraries (e.g. [0016]; [0027]; Figure 5; [0066] and [0109] (library of



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leucine zipper partners))), which read on the step of identifying a first and a second panel of proteins of **clms 2, 8, 12, 21 and 24**. The reference also teaches various libraries of proteins and/or combinatorial libraries as well as screening two libraries (e.g. [0075]+, especially, [0076] and [0078]), which read on the panels of proteins and libraries of proteins of **clms 2, 4, 5, 8, 12, 14, 21 and 24**.

The reference teaches conjugating various proteins to each of the two fragments (e.g. Claim 2; [0109]; Figures 1, [0071]), which read on method steps B-F of **clms 1-3, 8, 11-13, 17, 20, 21 and 24**.

The reference teaches detecting the fluorescent signal of the reconstituted GFP (e.g. [0110]+; Claim 22; Figure 6) and detecting protein interactions using fluorescent cell sorting (i.e. live cells) (e.g. [0071]; [0111]), which reads on the optically detectable and fluorescent signals of **clms 30-33 and 37**.

#### Discussion and Answer to Argument

12. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue the Hamilton reference is published later than the instant claimed priority dates (of the parent applications) and thus the Hamilton reference cannot be prior art references. (Reply, pp.24+).*

However, the instant claimed priority dates (of the parent applications, '412 and '885) are not granted as discussed supra.

Hamilton '599

13. Claims 1-5, 8, 11-14, 17, 20, 21, 24, and 30-33 are rejected under **35 U.S.C. 102(e)** as being anticipated by Hamilton et al (US 6,780,599; 8/24/2004; filed 5/14/2001; priority date 5/12/2000). The previous rejection over claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 is maintained for the reasons of record as set forth in the Office action as well as for the reasons below. The rejection over claim 37 is necessitated by applicant's amendment to the claims.

Hamilton et al, throughout the patent, teach a method of using GFP fragments to detect protein-protein interactions (Abstract). The reference teaches fragmenting GFP (e.g. col.9, lines 19+; claim 1), which reads on the generating first and second fragments of GFP of **clms 1-3, 8, 11-13, 17, 20, 21 and 24**.

The reference teaches attaching various proteins such as leucine zipper proteins and proteins encoded by cDNA libraries (e.g. col.3, lines 36+; Figure 5), which read on the step of identifying a first and a second panel of proteins of **clms 2, 8, 12, 21 and 24**. The reference also teaches various libraries of proteins and/or combinatorial libraries as well as screening two libraries (e.g. col.11, lines 54+, especially, col.12, lines 33+), which read on the panels of proteins and libraries of proteins of **clms 2, 4, 5, 8, 12, 14, 21 and 24**.

The reference teaches conjugating various proteins to each of the two fragments (e.g. Claim 1; Figures 1, col.12, lines 33+), which read on method steps B-F of **clms 1-3, 8, 11-13, 17, 20, 21 and 24**.

The reference teaches detecting the fluorescent signal of the reconstituted GFP (e.g. col.17, lines 55+; Claim 1; Figure 6) and detecting protein interactions using fluorescent cell

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sorting (i.e. live cells) (e.g. col.12, lines 33+); col.17, lines 55+), which reads on the optically detectable and fluorescent signals of **clms 30-33** and **37**.

Discussion and Answer to Argument

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue the Hamilton reference is published later than the instant claimed priority dates (of the parent applications) and thus the Hamilton reference cannot be prior art references. (Reply, pp.24+).*

However, the instant claimed priority dates (of the parent applications, '412 and '885) are not granted as discussed supra.

***Claim Rejections - 35 USC § 103***

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Umezawa WO and Hamilton '701

16. Claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al (PCT/JP00/09348; WO 02/08766; 1/31/02), in view of Hamilton et al (US 2002/0146701; 10/10/2002). (The complete WO document is in Japanese

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except for the Abstract. The English equivalent, US 20030003506 (a 371 of PCT/JP00/09348) is relied upon for the specific teaching of the said WO document. The relevant citations discussed above correspond to the US 20030003506 document.) The previous rejection over claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 is maintained for the reasons of record as set forth in the Office action as well as for the reasons below. The rejection over claim 37 is necessitated by applicant's amendment to the claims.

Umezawa et al, throughout the publication, teach methods of detecting protein and protein interactions for various proteins, as discussed above.

Umezawa et al do not explicitly teach the libraries of proteins.

However, Hamilton et al, throughout the publication, teach a method of using GFP fragments to detect protein-protein interactions, as discussed above. The reference teaches screening protein-protein interaction using various libraries of proteins, as discussed above.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to screen for protein-protein interactions using fragmented GFP fused to libraries of proteins.

A person of ordinary skill in the art would have been motivated at the time of the invention to fuse GFP fragments with libraries of proteins to screen for interactions, because Hamilton et al teach the need to detect protein-protein interactions from libraries of proteins.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the generating protein libraries and fusing library members with GFP fragments are known in the art such as the ones taught by Hamilton et al and Umezawa et al.

*Discussion and Answer to Argument*

17. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

*Applicants argue the cited references are published later than the instant claimed priority dates (of the parent applications) and thus the Hamilton reference cannot be prior art references. (Reply, pp.24+).*

However, the instant claimed priority dates (of the parent applications, '412 and '885) are not granted as discussed supra.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/  
Examiner, Art Unit 1639  
6/2/08

/Jon D. Epperson/  
Primary Examiner, AU 1639